Pergamon

Tetrahedron Letters 41 (2000) 1481–1482

TETRAHEDRON LETTERS

Synthesis of imbiline 1, a tetracyclic aza-aromatic alkaloid

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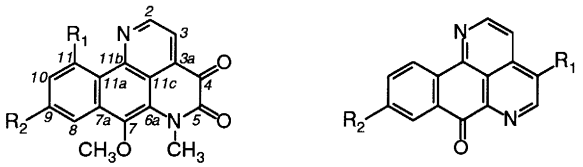
Received 10 November 1999; revised 29 November 1999; accepted 2 December 1999

Abstract

A tetracyclic aza-aromatic alkaloid, imbiline 1 (**1**) was synthesised from 1-amino-4-methoxynaphthalene hydrochloride (**7**) in seven steps.

Keywords: alkaloids; naphthyridines; oxidation; cyclisation.

A number of polycyclic aromatic alkaloids have been isolated from natural resources.[1] Imbilines 1 (**1**), 2 (**2**), 3 (**3**) and eupomatidines 1 (**4**), 2 (**5**), 3 (**6**) are tetracyclic aromatic alkaloids isolated from *Eupomatia bennettii* and *E. laurina* (Fig. 1).[2] We achieved total synthesis of **4**–**6** possessing iminoquinolinequinone structure.[3] Now we report the synthesis of **1**.



1: $R_1 = R_2 = H$
2: $R_1 = OH$, $R_2 = H$
3: $R_1 = H$, $R_2 = OCH_3$

4: $R_1 = H$, $R_2 = OCH_3$
5: $R_1 = OCH_3$, $R_2 = H$
6: $R_1 = R_2 = OCH_3$

Fig. 1.

1-Amino-4-methoxynaphthalene hydrochloride[4] (**7**) was treated with methyl vinyl ketone under acidic conditions to give benzo[*h*]quinoline (**8**) in 75% yield (Scheme 1). Oxidation of **8** using Vismara's method[5] afforded aldehyde (**9**) in 84% yield. The aldehyde (**9**) was treated with methyl methylsulfinylmethyl sulfide and sodium hydroxide followed by hydrochloric acid in ethanol[6] to furnish ethyl ester (**11**) in 60% yield.[7] Nitration of **11** was carried out with potassium nitrate and sulfuric acid–fuming sulfuric acid in nitromethane at −30°C to give 5-nitrobenzo[*h*]quinoline (**12**)[8] in 65% yield. Treatment of

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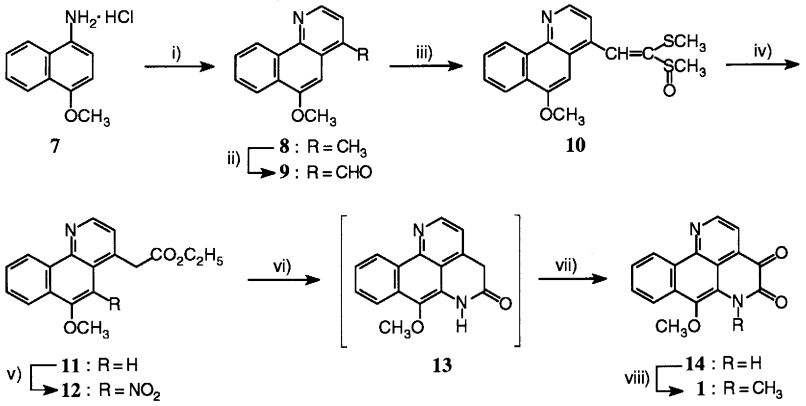
0040-4039/00/$ - see front matter
PII: S0040-4039(99)02322-9

12 with sodium hydrosulfite in aqueous tetrahydrofuran under argon formed 4,5-dihydronaphtho[1,2,3-*ij*][2,7]naphthyridin-5(6*H*)-one (**13**). We found that the benzylic position of the tetracyclic compound (**13**) was easily oxidised under air and a keto amide (**14**) was isolated in 62% yield from **12**. Finally **14** was methylated with methyl iodide in dimethylsulfoxide to furnish imbiline 1 (**1**) in 46% yield. The spectral data of synthetic compound **1**[9] and imbiline 1 obtained from natural resources were identical. The present method should be generally applicable for the synthesis of imbilines 2 (**2**) and 3 (**3**) possessing 4,5-dihydronaphtho[1,2,3-*ij*][2,7]naphthyridine-4,5(6*H*)-dione skeleton.



Scheme 1. (i) Methyl vinyl ketone, HCl, $ZnCl_2$, *m*-nitrobenzenesulfonic acid, ethanol, reflux, 3 h; (ii) trifluoroacetic acid, *tert*-butyl iodide, iodine, $FeCl_2 \cdot 4H_2O$, DMSO, 90°C, 12 h; (iii) methyl methylsulfinylmethyl sulfide, NaOH, 60°C, 1 h; (iv) HCl, ethanol, reflux, 3 h; (v) KNO_3, concentrated H_2SO_4–fuming H_2SO_4 (4:1), nitromethane, −30°C, 10 min; (vi) $Na_2S_2O_4$, tetrahydrofuran, H_2O, 25°C, 1 h; (vii) air oxidation; (viii) methyl iodide, KOH, DMSO, 25°C, 1 h.

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7. An attempted reaction of **8** with *n*-butyllithium in tetrahydrofuran followed by ethyl chloroformate failed, giving 2-(*n*-butyl)-6-methoxy-4-methylbenzo[*h*]quinoline in 76% yield.
8. Ethyl (6-methoxy-5-nitrobenzo[*h*]quinolin-4-yl)acetate (**12**): mp 129–131°C (yellow needles from ethanol). MS *m/z* (%): 340 (M^+, 1.6), 295 (27), 294 (100), 266 (84), 238 (22). Anal. calcd for $C_{18}H_{16}N_2O_5$: C, 63.53; H, 4.74; N, 8.23. Found: C, 63.73; H, 4.81; N, 8.14. IR (KBr): 1730, 1530, 1372 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ: 1.30 (3H, t, *J*=7.6 Hz, CH_2CH_3), 3.93 (2H, s, CH_2CO), 4.12 (3H, s, OCH_3), 4.22 (2H, q, *J*=7.6 Hz, CH_2CH_3), 7.43 (1H, d, *J*=4.6 Hz, C_3-H), 7.80–7.89 (2H, m, C_8-H, C_9-H), 8.17–8.20 (1H, m, C_7-H), 8.94 (1H, d, *J*=4.6 Hz, C_2-H), 9.38–9.42 (1H, m, C_{10}-H).
9. 7-Methoxy-6-methyl-4,5-dihydronaphtho[1,2,3-*ij*][2,7]naphthyridine-4,5(6*H*)-dione (imbiline 1 (**1**)): mp 237–240°C (red prisms from ethanol) [lit.[2] mp 212–214°C]. MS *m/z* (%): 292 (M^+, 98), 249 (100). High-resolution MS calcd for $C_{17}H_{12}N_2O_3$: 292.0848. Found: 292.0847. IR (KBr): 1694, 1670 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ: 3.97 (3H, s, OCH_3), 4.02 (3H, s, NCH_3), 7.78 (1H, td, *J*=7.3, 1.7 Hz, C_{10}-H), 7.83 (1H, td, *J*=7.3, 1.7 Hz, C_9-H), 8.24 (1H, dd, *J*=7.3, 1.7 Hz, C_8-H), 8.27 (1H, d, *J*=4.6 Hz, C_3-H), 9.21 (1H, dd, *J*=7.3, 1.7 Hz, C_{11}-H), 9.22 (1H, d, *J*=4.6 Hz, C_2-H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 35.87 (NCH_3), 62.97 (OCH_3), 118.02 (C_{11c}), 119.26 (C_3), 122.64 (C_{6a}), 122.73 (C_8), 125.05 (C_{11}), 128.30 (C_{10}), 130.17 (C_9), 130.33 (C_{11a}), 130.55 (C_{7a}), 132.00 (C_{3a}), 144.69 (C_7), 145.50 (C_{11b}), 148.64 (C_2), 157.72 (C_5), 176.68 (C_4).